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INVESTOR IN PEOPLE

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Dated 21 January 2005

Patents Form 1/77

Patents Act 1977
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030CT03 E841812-1 B16678
P01/7700 0.00-0323137.0

THE PATENT OFFICE
J
- 3 OCT 2003
NEWPORT

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

2. Patent application number
(The Patent Office will fill this part in) 0323137.0

- 3 OCT 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

LISA C.W. CHANG - 8726259001
ADRIAAN P. IJZERMAN - 8726267001
8726275001 - JOHANNES BRUSSEE
LEIDEN UNIVERSITY

SEE ATTACHED SHEET FOR ADDRESS AND POSTCODE OF EACH APPLICANT

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation 8726283001

4. Title of the invention

2,4,6- TRISUBSTITUTED PYRIMIDINES AND THEIR DIFFERENT USES

5. Name of your agent *(if you have one)* N/A

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

229 KINGS ROAD
CHORLTON-CUM-HARDY
MANCHESTER
M21 0XG

Patents ADP number *(if you know it)* 8726267002

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
N/A		

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

N/A

Number of earlier UK application

Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

YES

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	1
Description	33
Claim(s)	
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for a preliminary examination and search (Patents Form 9/77)	
Request for a substantive examination (Patents Form 10/77)	
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature(s) [signature] Date 30/9/2003

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

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Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered YES in part 8, a Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.

NAMES, ADDRESS AND POSTCODE OF EACH APPLICANT:

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2,4,6-TRISUBSTITUTED PYRIMIDINES AND THEIR DIFFERENT USES

FIELD OF INVENTION

This invention relates to 2,4,6-trisubstituted pyrimidines, pharmaceutical compositions containing them and the uses thereof.

BACKGROUND OF THE INVENTION

The endogeneous neuromodulator adenosine acts extracellularly via activation of specific membrane-bound receptors called P_1-purinoceptors. These adenosine receptors are divided into four subclasses, A_1, A_{2A}, A_{2B} and A_3 receptors. All four classes are coupled to the enzyme adenylate cyclase. Activation of the adenosine A_1 and A_3 receptors can lead to an inhibition of adenylate cyclase, while activated A_{2A} and A_{2B} receptors can stimulate adenylate cyclase. The adenosine receptors are ubiquitously distributed throughout the body, and can modulate diverse physiological functions, including induction of sedation, relaxation of smooth muscle and vasodilation. Activation of these receptors by adenosine can therefore be of importance in many disease states. Accordingly, blocking these receptors can produce an effect leading to the prevention or treatment of many diseases. For example, the A_{2A} adenosine receptor antagonists are reported to have a beneficial effect on neurodegenerative diseases such as Parkinson's disease.[1]

In recent years, a number of new and interesting ligands which block the various adenosine receptor subtypes have been synthesised. These ligands encompass an ever-expanding area of bi- and tri-cyclic heteroaromatic systems - featuring 3-nitrogen tri-cyclic systems (e.g., the imidazoquinolines);[2] 4-nitrogen tri-cyclic systems (e.g.,

triazoloquinoxalines);[3] 6-nitrogen tri-cyclic systems (e.g., the pyrazolotriazolopyrimidines);[4] 2-nitrogen bi-cyclic systems (e.g., the naphthyridines);[5] and 3-nitrogen bi-cyclic systems (e.g., deazaadenines)[6] to name but a few groups. Indeed a recent review[7] states quite clearly that the different structural classes for A_1 adenosine receptor antagonists are bi-and tri-cyclic heterocyclic compounds. More recently, an investigation in our group highlighted the general low affinity of mono-cyclic compounds.[8]

LIST OF PERTINENT PRIOR ART

The following is a list of prior art which is considered to be pertinent for describing the state of the art in the field of the invention, all of which are also included in the list of publications provided hereinafter. Acknowledgements of these references herein will be made by indicating the number from the said list of publications which is also indicated in brackets below.

[1] Fredholm, B. B.; IJzerman, A. P.; Jacobson, K. A.; Klotz, K.-N.; Linden, J. International Union of Pharmacology. XXV. Nomenclature and Classification of Adenosine Receptors. *Pharmacological Reviews* **2001**, *53*, 527-552.

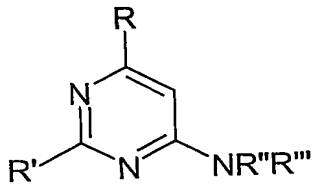
[7] Müller, C. E. A_1 Adenosine Receptors and their Ligands: Overview and Recent Developments. *Il Farmaco* **2001**, *56*, 77-80.

[12] Soudijn, W.; van Wijngaarden, I.; IJzerman, A. P. Medicinal Chemistry of Adenosine A_1 Receptor Ligands *Current Topics in Medicinal Chemistry* **2003**, *3*, 355-367.

[13] Müller, C. E., Stein, B. Adenosine Receptor Antagonists: Structures and Potential Therapeutic Applications *Current Pharmaceutical Design* **1996**, *2*, 501-530.

SUMMARY OF THE INVENTION

The present invention is based on the discovery that the compounds of general formula (I) are surprisingly highly potent compounds which may be used to treat adenosine receptor mediated conditions. This invention provides a compound of the general formula (I):



(I)

wherein

R represents hydrogen (except when R' = H), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl;

R' represents hydrogen (except where R = H), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl;

R'' represents hydrogen, acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl;

R''' represents hydrogen, acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl;

R'' and R''' can also together form a substituted or unsubstituted heterocyclic ring or heterocyclic rings.

or a salt of said compound.

The term '***adenosine receptor mediated conditions***' is intended to include disease states or conditions characterised by their responsiveness to treatment with an adenosine receptor mediating compound, e.g. a 2,4,6-trisubstituted pyrimidine derivative as described by general formula (I), where the treatment causes a significant diminishment of at least one symptom or effect of the state achieved with an adenosine receptor mediating compound of the invention.

By the term '***alkyl***' it is meant any saturated hydrocarbon, either branched or unbranched comprising from 1 to about 30 carbon atoms. This includes straight-chained alkyl groups, branched-chained alkyl groups, cycloalkyl (alicyclic) groups, alkyl-substituted cycloalkyl groups, and cycloalkyl-substituted alkyl groups. The term further includes alkyl groups, which can further include oxygen, nitrogen, sulphur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In preferred embodiments, a straight or branched chain has 30 or fewer carbon atoms in its backbone, and more preferably 20 or fewer. Likewise, preferred cycloalkyls have from 3-10 carbons, and more preferably 3, 4, 5, 6, 7 carbons in the ring-structure.

The term '***acyl***' refers to compounds of the kind '***C(O)X***' where ***X*** in turn represents hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl.

The term '-$(CH_2)_n$-***aryl***' means a short straight alkyl chain between the (substituted) aryl group and the drawn structure, where n can equal 0 up to and including 10.

The term '***aryl***' as used herein, refers to aromatic groups which can include 5- and 6-membered single-ring groups, with 0 to 4 heteroatoms, for example benzene, pyrrole, furan, thiophene, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Aryl groups can also include polycyclic fused aromatic groups such as naphthyl, quinolyl, indolyl, benzoxazole, benzothiazole and the like. Those aryl groups containing heteroatoms may also be referred to as heteroaryls or heteroaromatics. The aromatic ring may be substituted at one or more ring positions, with such substituents as described herein. Aryl groups can also be fused or bridged with alicyclic or heteroalicyclic rings which are not aromatic.

The term '***substituted***' is intended to include substituents replacing hydrogen on one or more of the carbons of a moiety. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkyloxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkyoxyl, phosphate, phosphonate, phosphinato, cyano, amino (including alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino), acylamino, (including alkylcarbonylamino, arylcarbonylamino, carbamyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. It will be understood to those skilled in the art that the moieties substituted on the (unsaturated and saturated) carbon chain can themselves be substituted, if appropriate.

The term '***heteroatom***' refers to an atom of any element other than carbon or hydrogen. Preferred heteroatoms are oxygen, nitrogen, sulphur and phosphorus.

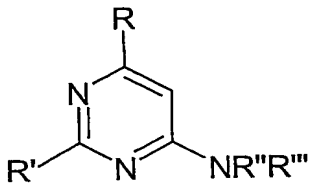
The terms '***alkenyl***' and '***alkynyl***' refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively.

When referring to ***salts*** of the compound of the present invention it is meant any physiologically acceptable salt. The term '***physiologically acceptable salt***' refers to any non-toxic alkali metal, alkaline earth metal, and ammonium salts commonly used in the pharmaceutical industry, including the sodium, potassium, lithium, calcium, magnesium, barium ammonium and protamine zinc salts, which are prepared by methods known in the art. The term also includes non-toxic ***acid addition salts***, which are generally prepared by reacting the compounds of this invention with a suitable organic or inorganic acid. The acid addition salts are those which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable. Examples include those derived from mineral acids, and include, *inter alia*, hydrochloride, hydrobromic, sulphuric, nitric phosphoric, metaphosphoric and the like. Organic acids include, *inter alia*, tartaric, acetic, proprionic, citric, malic, malonic, lactic, fumaric, benzoic, cinnamic, mandelic, glycolic, gluconic, pyruvic, succinic, salicylic and arylsulfonic, e.g. p-toluenesulfonic, acids.

According to one embodiment of the invention, the substituent R represents hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl,

R' represents hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl, R'' represents hydrogen, acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl, R''' represents hydrogen, acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl, R'' and R''' can also together form a substituted or unsubstituted heterocyclic ring or heterocyclic rings.

Yet further, the invention relates to a pharmaceutical composition comprising as active ingredient an effective amount of a compound of the general formula (I):

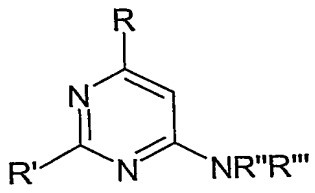


(I)

or a salt of said compound, wherein R, R', R'', R''' are as defined herein before.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the development of several novel adenosine receptor antagonists. Thus, the present invention details compounds of the general formula (I):



(I)

wherein

R represents hydrogen (except when R' = H), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl;

R' represents hydrogen (except where R = H), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl;

R'' represents hydrogen, acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl;

R''' represents hydrogen, acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl;

R'' and R''' can also together form a substituted or unsubstituted heterocyclic ring or heterocyclic rings.

or a salt of said compound.

More particularly, the present invention provides compounds of general formula (I), wherein the substituents are as follows:

R represents a hydrogen (except when R' = H), alkyl, (substituted) -$(CH_2)_n$-aryl;

R' represents a hydrogen (except when R' = H), alkyl, (substituted) -$(CH_2)_n$-aryl;

R'' represents a hydrogen, acyl, (substituted) alkyl, (substituted) -$(CH_2)_n$-aryl;

R''' represents a hydrogen, acyl, (substituted) alkyl, (substituted) -$(CH_2)_n$-aryl;

R'' and R''' can also together form a substituted or unsubstituted heterocyclic ring or heterocyclic rings;

or a salt of said compound.

According to yet another preferred embodiment, the compound of the present invention is that wherein

R represents a (substituted) -$(CH_2)_n$-aryl;

R' represents a (substituted) -$(CH_2)_n$-aryl;

R" represents a hydrogen, methyl;

R''' represents an acyl;

or a salt of said compound.

According to yet another preferred embodiment, the compound of the present invention is that wherein

R represents a (substituted) -$(CH_2)_n$-aryl;

R' represents a (substituted) -$(CH_2)_n$-aryl;

R" represents an acyl;

R''' represents a hydrogen, methyl;

or a salt of said compound.

According to one preferred embodiment, the compound of the present invention is that wherein

R represents a phenyl;

R' represents a phenyl;

R'' represents a hydrogen, methyl;

R''' represents an acyl;

or a salt of said compound.

According to one preferred embodiment, the compound of the present invention is that wherein

R represents a phenyl;

R' represents a phenyl;

R'' represents an acyl;

R''' represents a hydrogen, methyl;

or a salt of said compound.

According to yet another preferred embodiment, the compound of the present invention is that wherein

R represents a (substituted) alkyl;

R' represents a (substituted) alkyl;

R" represents a hydrogen, methyl;

R''' represents an acyl;

or a salt of said compound.

According to yet another preferred embodiment, the compound of the present invention is that wherein

R represents a (substituted) alkyl;

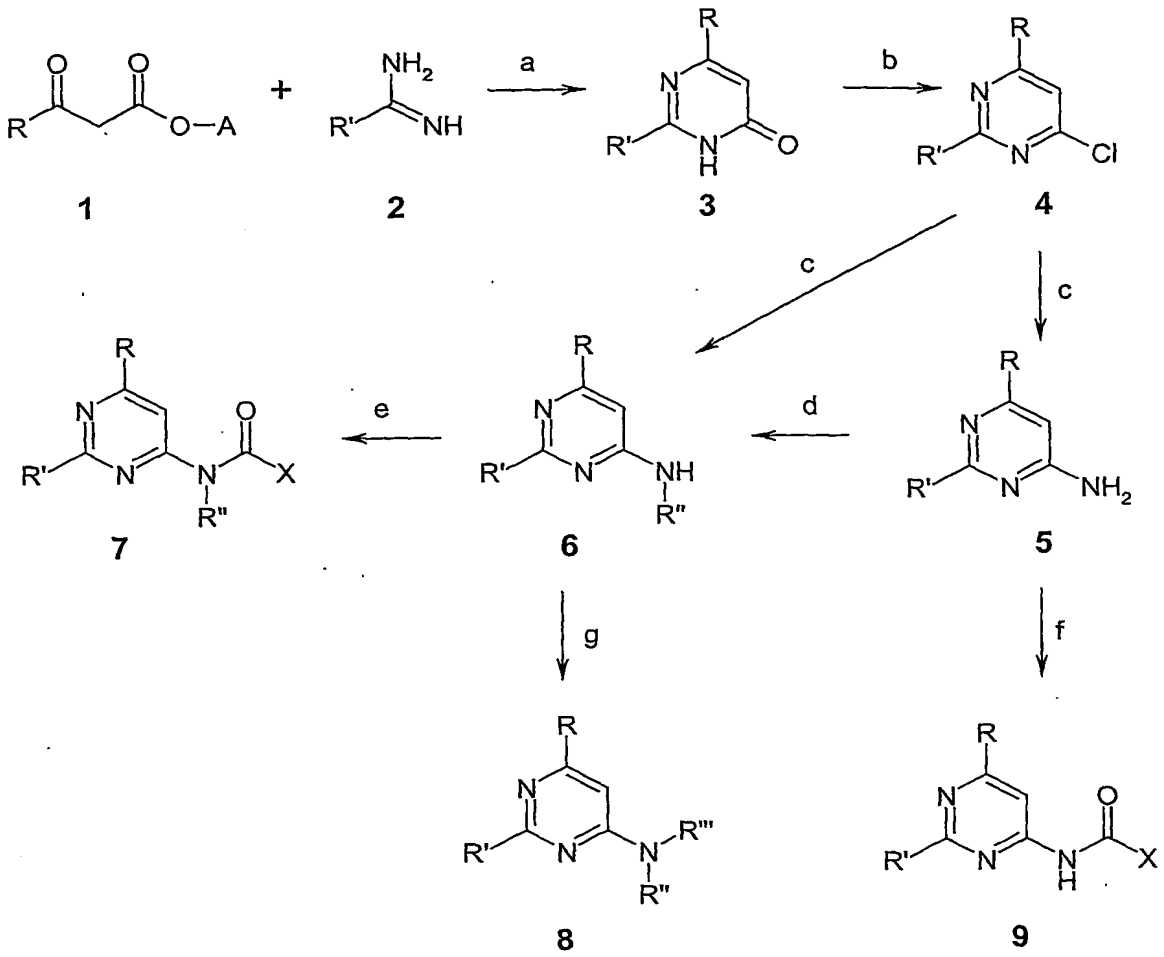
R' represents a (substituted) alkyl;

R" represents an acyl;

R''' represents a hydrogen, methyl;

or a salt of said compound.

The compounds of the present invention may be prepared by several synthetic procedures. For example, the synthesis route to obtain some 2,4,6-trisubstituted derivatives is depicted in the scheme herein below:



Scheme 1: (a) NaOH, EtOH; (b) $POCl_3$; (c) NHR'', sealed vessel, 140°C; (d) R''CHO, $NaBH(OAc)_3$, CH_2Cl_2; (e) and (f) XC(O)Cl, Et_3N, 1,4-dioxane or XC(O)OH, standard peptide coupling agent (e.g. EDC), HOBt, DMF; (g) R'''CHO, $NaBH(OAc)_3$, CH_2Cl_2.

According to this scheme, the synthesis started with reacting a β-ketoester with an amidine in the presence of sodium hydroxide in ethanol at room temperature to create the pyrimidinone (3) in a 60% yield.[9] This was in turn reacted with phosphorous oxychloride

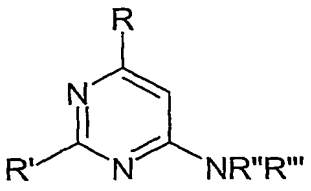
to give the halogenated pyrimidine (4).[10] Displacement of the chloride with an amine gave, in the case of ammonia gas, the primary amine (5), and the substituted secondary amines (6) in the case of primary amines. Compound (6) could also be obtained with reductive alkylation with the appropriate aldehyde from compound (5); as could compound (8) from (6). For the final step to create acyls (7) and (9), the appropriate carboxylic acid/acid chloride was used, in the presence of a base (and in some cases a coupling agent), to react with the amines (6) and (5). Where R'' = R''', then compound (8) could be made from compound (5) with 2 equivalents of the appropriate alkyl iodide and base.

As will be detailed in Table 2, the compounds of the present invention are *biologically active.*

The term '***biologically active***' indicates that the compound of the present invention has some sort of a biological activity, for example, a measurable effect on a target receptor. As will be detailed hereinafter, the compound of the present invention may block the biological action of adenosine receptors, thus acting as adenosine receptor antagonists.

The term '***antagonist***' used herein refers to a molecule that binds to a receptor without activating the receptor. It competes with the endogeneous ligand for this binding site and, thus reduces the ability of the endogeneous ligand to stimulate the receptor.

Thus, the invention also provides pharmaceutical compositions comprising as active ingredient an effective amount of one or more of a compound of the general formula (I):



(I)

wherein

R represents hydrogen (except when R' = H), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl;

R' represents hydrogen (except where R = H), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl;

R'' represents hydrogen, acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl;

R''' represents hydrogen, acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) -$(CH_2)_n$-aryl;

R'' and R''' can also together form a substituted or unsubstituted heterocyclic ring or heterocyclic rings.

or a salt of said compound.

The term '***effective amount***' for the purposes described herein is that determined by such considerations as are known to those versed in the art. The amount must be sufficient to achieve a desired therapeutic effect, e.g. to treat a disease or disorder.

The terms '***treat***', '***treating***' and '***treatment***' refer to the administering of a therapeutic amount of the compound or composition of the present invention which is effective to ameliorate undesired symptoms associated with a disease, to prevent the manifestation of such symptoms before they occur, to slow down the progression of a disease, to slow down the deterioration of symptoms, to slow down the irreversible damage caused by the chronic stage of a disease, to lessen the severity of, or cure a disease, to improve survival rate or more rapid recovery, to prevent the disease from occurring, or a combination of two or more of the above.

The terms '***modulate***', '***modulation***', and '***modulation***' are intended to include preventing, eradicating, or inhibiting the resulting increase of undesired physiological activity associated with the stimulation of an adenosine receptor, e.g. in the context of the therapeutic methods of this invention. In another embodiment, the term '***modulate***' includes antagonistic effects, e.g. diminishment of the activity or production of mediators which result from the (over)-stimulation of adenosine receptor(s).

The disease is preferably associated with the biological action of one or more adenosine receptors wherein the compound of the present invention acts as an adenosine receptor antagonist. For example antagonists of A_1 receptors have been implicated as compounds which may be used in the treatment of cardiac, renal and sleep disorders.

The pharmaceutical composition of the present invention may further comprise *pharmaceutically acceptable additives*.

Further, the term '***pharmaceutically acceptable additives***' used herein refers to any substance combined with said compound and include, without being limited thereto, diluents, excipients, carriers, solid or liquid fillers or encapsulating materials which are typically added to formulations to give them a form or consistency when it is given in a specific form, e.g. in tablet form, as a simple syrup, aromatic powder, and other various elixirs. The additives may also be substances for providing the formulation with stability, sterility and isotonicity (e.g. antimicrobial preservatives, antioxidants, chelating agents and buffers), for preventing the action of microorganisms (e.g. antimicrobial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid and the like) or for providing the formulation with an edible flavour, etc.

Preferably, the additives are inert, non-toxic materials, which do not react with the active ingredient of the invention. Yet, the additives may be designed to enhance the binding of the agent to its receptor. Further, the term *additive* may also include adjuvants, which, by definition, are substances affecting the action of the active ingredient in a predictable way.

The additive can be any of those conventionally used and are only limited by chemico-physical considerations, such as solubility and lack of reactivity with the compound of the invention, and by route of administration.

The active agent of the invention may be administered orally to the patient. Conventional methods such as administering the compound/s in tablets, suspensions, emulsions, capsules, powders, syrups and the like are usable.

For oral administration, the composition of the invention may contain additives for facilitating oral delivery of the compound/s of the invention. Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatine type containing, for example surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatine, guar gum, colloidal silicon dioxide, croscarmellose sodium talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, and pharmacologically compatible carriers. Lozenge forms can comprise the active agent in a flavour, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatine and glycerine, or sucrose and acacia, emulsions, gels, and the like. Such additives are known in the art.

Alternatively, the compound/s may be administered to the patient parenterally. In this case, the composition will generally be formulated in a unit dosage injectable form (solution, suspension, emulsion). Pharmaceutical formulation suitable for injection may

include sterile aqueous solutions or dispersions and sterile powders for reconstitution into sterile injectable solutions or dispersions. The carrier can be a solvent or dispersing medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, lipid polyethylene glycol and the like), suitable mixtures thereof and vegetable oils.

Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Non-aqueous vehicles such as cottonseed oil, sesame oil, olive oil, soybean oil, corn oil, sunflower oil, or peanut oil and ester, such as isopropyl myristate, may also be used as solvent systems for the composition of the present invention.

Suitable fatty acids for the use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

Suitable detergents for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefinic sulfonates, alkyl, olefin, ether and monoglyceride sulfates, and sulfosuccinates, (c) non-ionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxy-ethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-ß-aminopropionates, and 2-alkyl-imidazoline quarternary ammonium salts, and mixtures thereof.

Further, in order to minimise or eliminate irritation at the site of injection, the compositions may contain one or more non-ionic surfactants having a hydrophile-lipophile balance (HLB) from about 12 to about 17. Suitable surfactants include polyethylenesorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The choice of an additive will be determined in part by the particular compound of the present invention, as well as by the particular method used to administer the composition.

Notwithstanding the above, the composition of the present invention may include one or more of the compounds of the present invention and may compromise other biologically active substances, to provide a combined therapeutic effect.

The compounds and compositions of the present invention as set forth hereinabove and below are administered and dosed in accordance with good medical practice, taking into account the clinical conditions of the individual patient, the site and method of administration, scheduling of administration, individual's age, sex, body weight and other factors known to medical practitioners.

The dose may be single doses or multiple doses over a period of several days. The treatment generally has a length proportional to the length of the disease process and drug effectiveness and the individual species being treated. Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to those of ordinary skill in the art. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments, until the optimum effect under the circumstances is reached. Exemplary

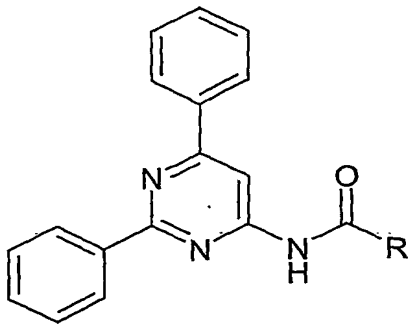
dosages range from about 0.01mg/kg body weight to about 10 mg/kg body weight of the subject being treated per day.

The invention has been described in an illustrative manner, and it is to be understood that the terminology which has been used, is intended to be in the nature of words of description rather than of limitation. Obviously, many modifications and variations of the present invention are possible in light of the above teaching. It is therefore, to be understood that within the scope of the appended claims, the invention may be practised otherwise than as specifically described hereinafter.

Throughout this application various publications are referred to by a number. Full citations for the publications are listed hereinafter. The disclosure of these publications in their entireties is hereby incorporated by reference into the application in order to more fully describe the state of the art to which this invention pertains.

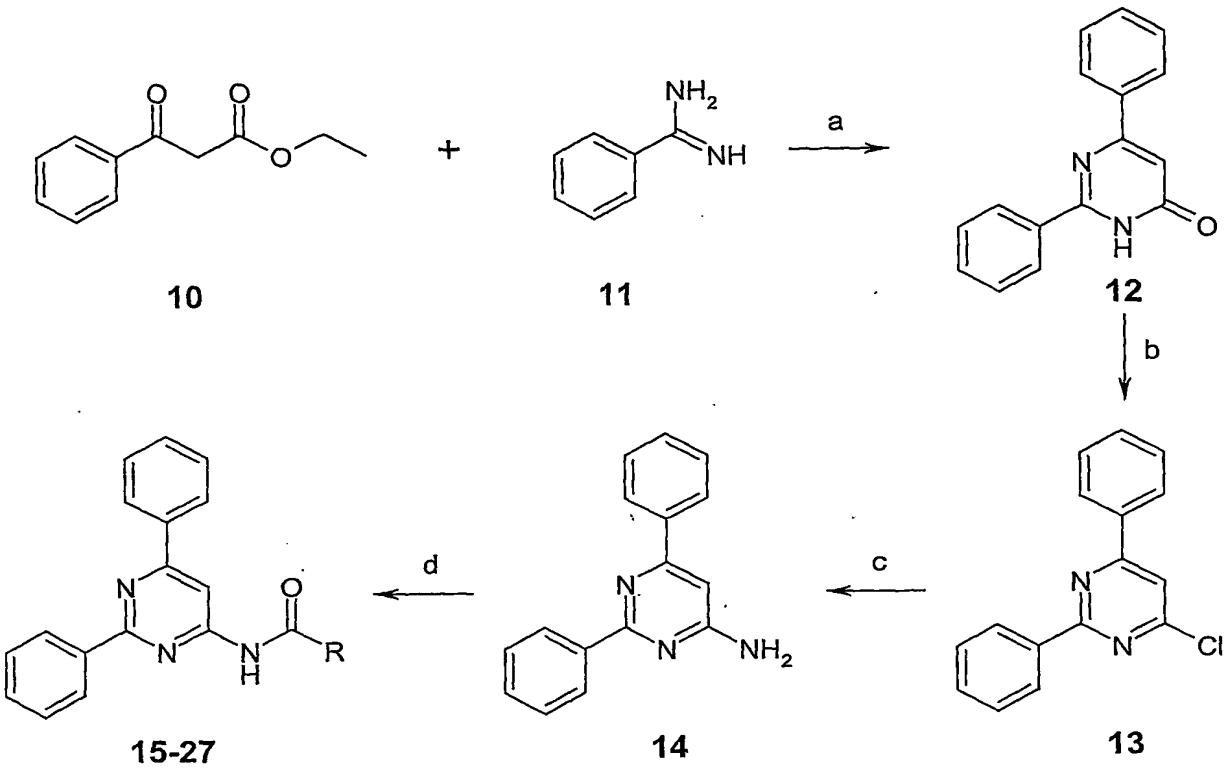
SPECIFIC EXAMPLES – 2,6-Diphenyl-4-carboxyamidopyrimidines

This invention is further described in the following specific examples, which do not limit the scope of the invention described in the claims.



(II)

The examples detailed here of the general formula (II) are synthesised according to the route detailed below in Scheme 2.



Scheme 2: (a) NaOH, EtOH, H_2O; (b) $POCl_3$, PCl_5; (c) NH_3 in EtOH, sealed vessel, 140 °C; (d) RC(O)Cl, Et_3N, 1,4-dioxane.

Chemistry – General

Chemicals and Solvents All reagents were obtained from commercial sources and all solvents were of an analytical grade.

Chromatography Thin-layer chromatography (TLC) was carried out using Merck silica gel plastic backed F_{254} plates, visualised under UV (254 nm).

Instruments and Analysis Elemental analyses were performed for C,H,N (Leiden Institute of Chemistry, Leiden University, The Netherlands). ^1H and ^{13}C NMR spectra

were recorded on a Bruker AC 200 (^{1}H NMR, 200MHz; ^{13}C NMR, 50.29 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm (δ) relative to this. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Mass Spectra were measured on a Finnigan MAT TSQ-70 spectrometer equipped with an electrospray interface for ESI experiments. Spectra were collected by constant infusion of the analyte dissolved in methanol. ESI is a soft ionisation techinique resulting in protonated, sodiated species in positive ionisation mode and deprotonated species in the negative ionisation mode.

Synthetic Procedures

2,6-Diphenyl-3H-pyrimidin-4-one (12)[9]

Benzamidine hydrochloride (3.9 g, 24.9 mmol) was dissolved in a minimal amount of H_2O (10 mL), to this was added sodium hydroxide pellets (1.0 g, 24.9 mmol, 1 eq.) dissolved in H_2O (2 mL), followed by ethylbenzoate (4.53 mL, 26.1 mmol, 1.05 eq.). Ethanol was then added until a clear solution was obtained. The reaction mixture was then allowed to stir at room temperature overnight yielding a thick suspension, which was then filtered to give a white solid. After washing with diethyl ether to remove unreacted/excess ß-ketoester the solid was dried *in vacuo* to give 57% of the desired product. ^{1}H NMR δ (DMSO-d6): 8.31-8.18 (m, 5H, Ar), 7.60-7.54 (m, 5H, Ar), 6.92 (s, 1H, Ar).

4-Chloro-2,6-diphenyl-pyrimidine (13)[10]

Phosphorous oxychloride (9.30 mL, 99.8 mmol, 7.5 eq.) was added dropwise to 2,6-diphenyl-3H-pyrimidin-4-one (**12**) (3.3 g, 13.3 mmol) in a vigorous reaction. To this mixture was added slowly phosphorous pentachloride (2.77 g, 13.3 mmol, 1 eq.) and the reaction mixture was stirred at reflux for 3 hours. The reaction mixture was then quenched by pouring into ice-water, and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$) and then concentrated to give a yellow solid. This was recrystallised from hot ethanol to give fine white needles (65%). ^{1}H NMR δ ($CDCl_3$): 8.60-8.18 (m, 5H, Ar), 7.63 (s, 1H, Ar), 7.51-7.57 (m, 5H, Ar).

2,6-Diphenyl-pyrimin-4-ylamine (14)

Ethanol (50 mL) was saturated with $NH_{3(g)}$ at 0 °C and added to 4-chloro-2,6-diphenyl-pyrimidine (**2**) (2.30 g, 8.63 mmol) in a sealed vessel. This was then stirred at 140 °C for 24 h. Upon cooling and concentrating, the residues were extracted with hot chloroform (3 x 50 mL) and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography on SiO_2 eluting with CH_2Cl_2 to give an off-white solid (80%). ^{1}H NMR δ (DMSO-d6): 8.47-8.42 (m, 2H, Ar), 8.16-8.13 (m, 2H, Ar), 7.57-7.5 (m, 6H, Ar), 7.02 (br s, 2H, N*H*$_2$), 6.88 (s, 1H, Ar).

General Procedure for the Preparation of 4-Amido-2,6-diphenylpyrimidines (15-27)

To a solution of 4-amino-2,6-diphenylpyrimidine (0.202 mmol, 1 eq.) in 1,4-dioxane (5mL) was added triethylamine (0.223 mmol, 1.1 eq.), followed by the appropriate acid

chloride (0.304 mmol, 1.5 eq.). This was then stirred at reflux until no starting material was visible by TLC. Upon completion, the reaction mixture was separated between ethyl acetate (20 mL) and water (20 mL). The aqueous layer was further extracted with ethyl acetate (2 × 20 mL) and the combined organics washed with water and brine. After drying over $MgSO_4$ and evaporation under reduced pressure, the crude product was purified by column chromatography, eluting with a petroleum ether-ethyl acetate or a dichloromethane-methanol solvent system. Recrystallisation with ethanol or petroleum ether-ethyl acetate gave the corresponding amide in crystalline form.

N-(2,6-Diphenyl-pyrimidin-4-yl)-benzamide (15). Yield 48%; white solid; mp 120-123 °C; ^{1}H NMR δ ($CDCl_3$): 8.78 (bs, 1H, N-*H*), 8.72 (s, 1H, pyrimidine-*H*), 8.58-8.54 (m, 2H, phenyl-*H*), 8.34-8.29 (m, 2H, phenyl-*H*), 7.99-7.96 (m, 2H, phenyl-*H*), 7.64-7.48 (m, 9H, phenyl-*H*). ^{13}C-NMR δ($CDCl_3$): 166.2, 165.9, 164.0, 158.4, 137.3, 137.1, 133.4, 132.6, 130.8, 130.7, 128.9, 128.7, 128.3, 128.1, 127.4, 127.2, 103.3. MS (ES^+): 351.57, 373.55 Da. Anal. ($C_{23}H_{17}N_3O.0.25H_2O$) C, H, N.

N-(2,6-Diphenyl-pyrimidin-4-yl)-acetamide (16). Yield 43%; white solid; mp 140 °C; ^{1}H NMR δ ($CDCl_3$): 8.54-8.49 (m, 3H, phenyl-*H* + pyrimidinyl-*H*) 8.45 (s, 1H, N-*H*), 7.55-7.49 (m, 6H, phenyl-*H*), 2.20 (s, 3H, C*H*$_3$)ppm. ^{13}C-NMR δ($CDCl_3$): 165.9, 158.1, 154.3, 140.7, 130.74, 130.68, 128.7, 128.4, 128.0, 127.4, 103.0, 35.7ppm. MS (ES^+): 289.89 Da. Anal. ($C_{18}H_{15}N_3O.0.50EtOH$) C, H, N.

N-(2,6-Diphenyl-pyrimidin-4-yl)-propionamide (17). Yield 77%; white solid; mp 125-126 °C; ^{1}H-NMR δ($CDCl_3$): 8.58 (s, 1H, pyrimidinyl-*H*), 8.55-8.50 (m, 2H, phenyl-*H*), 8.36 (bs, 1H, N*H*), 8.30-8.25 (m, 2H, phenyl-*H*), 7.54-7.49 (m, 6H, phenyl-*H*), 2.41(q, 2H, J= 7.3 Hz, C*H*$_2$CH$_3$), 1.23 (t, 2H, -CH$_2$C*H*$_3$)ppm. ^{13}C-NMR δ($CDCl_3$):

173.2, 165.8, 163.9, 137.3, 137.0, 130.7, 128.7, 128.0, 127.4, 121.5, 103.1, 30.7, 8.87ppm. MS (ES^+): 303.8 Da. Anal. calc. for $C_{19}H_{17}N_3O$ (C 75.23; H 5.65; N 13.85) found (C 75.32; H 6.23; N 14.04) %.

N-(2,6-Diphenyl-pyrimidin-4-yl)-butyramide (18). Yield 53%; white solid; mp.102-103 °C. ^{1}H-NMR $\delta(CDCl_3)$: 8.60 (bs, 2H, pyrimidine-*H* + N*H*), 8.56-8.51 (m, 2H, phenyl-*H*), 8.31-8.26 (m, 2H, phenyl-*H*), 7.45-7.50 (m, 6H, phenyl-*H*), 2.29 (t, 2H, J = 7.48 Hz, C*H*$_2$CH$_2$CH$_3$), 1.71 (sextet, 2H, J = 7.39 Hz, CH$_2$C*H*$_2$CH$_3$), 0.95 (t, 3H, J = 7.30 Hz, CH$_2$CH$_2$C*H*$_3$)ppm. ^{13}C-NMR $\delta(CDCl_3)$: 172.9, 165.8, 163.8, 158.5, 137.4, 137.0, 130.8, 130.7, 128.6, 128.4, 128.1, 127.3, 103.3, 39.2, 18.3, 13.5ppm. MS (ES^+): 317.87 Da. Anal. ($C_{20}H_{19}N_3O$. 0.14H_2O) C, H, N.

N-(2,6-Diphenyl-pyrimidin-4-yl)-isobutyramide (19). Yield 48%; white solid; mp 116-117 °C. ^{1}H-NMR $\delta(CDCl_3)$: 8.59 (s, 1H, pyrimidine-*H*), 8.55-8.50 (m, 2H, phenyl-*H*), 8.30-8.25 (m, 2H, phenyl-*H*), 8.05 (bs, 1H, N*H*), 7.54-7.49 (m, 6H, phenyl-*H*), 2.64 (septet, 1H, J = 6.85 Hz, C*H*(CH$_3$)$_2$), 1.33 (d, 6H, J = 6.94 Hz, CH(C*H*$_3$)$_2$)ppm. ^{13}C-NMR $\delta(CDCl_3)$: 176.5, 165.8, 158.3, 137.4, 137.1, 130.7, 128.7, 128.4, 128.0, 127.4, 103.4, 36.8, 19.2, 19.1ppm. MS (ES^+): 317.94, 634.75 Da. Anal. ($C_{20}H_{19}N_3O$. 0.1H_2O).

N-(2,6-Diphenyl-pyrimidin-4-yl)-3-methyl-butyramide (20). Yield 52%, white solid. mp. 127°C. ^{1}H-NMR $\delta(CDCl_3)$: 8.59 (s, 1H, pyrimidinyl-*H*), 8.56-8.51 (m, 2H, phenyl-*H*), 8.35 (bs, 1H, N*H*), 8.31-8.26 (m, 2H, phenyl-*H*), 7.56-7.49 (m, 6H, phenyl-*H*), 2.25-2.24 (m, 3H, C*H*$_2$C*H*(CH$_3$)$_2$), 1.02-0.99 (d, 6H, CH$_2$CH(C*H*$_3$)$_2$)ppm. ^{13}C-NMR $\delta(CDCl_3)$: 172.1, 165.9, 158.2, 137.4, 137.1, 130.7, 130.6, 128.6, 128.4, 128.0, 127.4, 113.5, 103.2, 46.8, 25.8, 22.3ppm. MS (ES^+): 331.8 Da. Anal. ($C_{21}H_{21}N_3O$).

N-(2,6-Diphenyl-pyrimidin-4-yl)-2-ethyl-butyramide (21). Yield 58%, white solid. mp. 137-138 °C. ^{1}H-NMR $\delta(CDCl_3)$: 8.64 (s, 1H, pyrimidine-*H*), 8.55-8.50 (m, 2H, phenyl-*H*), 8.31-8.26 (m, 2H, phenyl-*H*), 8.09 (bs, 1H, N*H*), 7.54-7.49 (m, 6H, phenyl-*H*), 2.23-2.11 (m, 1H, C*H*$(CH_2CH_3)_2$), 1.86-1.56 (m, 4H, CH(C*H*$_2$CH$_3$)$_2$), 0.99 (t, 6H, J = 7.31 Hz, CH$(CH_2CH_3)_2$)ppm. ^{13}C-NMR $\delta(CDCl_3)$: 175.8, 165.9, 158.3, 130.8, 130.7, 128.7, 128.4, 128.1, 127.4, 121.6, 103.2, 52.2, 25.5, 11.8ppm. MS (ES^+): 345.86, 690.56 Da. Anal. ($C_{22}H_{23}N_3O$. $0.1H_2O$).

N-(2,6-Diphenyl-pyrimidin-4-yl)-2-methyl-butyramide (22), Yield 89%, white solid. mp.: 102 °C. ^{1}H-NMR $\delta(CDCl_3)$: 8.71 (br s, 1H, N-*H*), 8.67 (s, 1H, pyrimidyl-*H*), 8.59-8.54 (m, 2H, aromatic-*H*), 8.33-8.28 (m, 2H, aromatic-*H*), 7.53-7.50 (m, 6H, aromatic-*H*), 2.29-2.19 (m, 1H, CH), 1.82-1.86 (m, 1H, 0.5*C*H*$_2$), 1.55-1.41 (m, 1H, 0.5*C*H*$_2$), 1.16 (d, J=6.58Hz, 3H, C*H*$_3$), 0.90 (t, J=7.30Hz, 3H, C*H*$_3$) ppm. ^{13}C-NMR $\delta(CDCl_3)$: 176.4, 165.9, 163.9, 158.5, 137.4, 137.1, 130.8, 130.7, 128.7, 128.4, 128.1, 127.4, 103.3, 44.0, 27.0, 16.9, 11.6 ppm. MS (ES^+): 331.8 (MH^+) Da. Anal. ($C_{21}H_{21}N_3O$).

N-(2,6-Diphenyl-pyrimidin-4-yl)-2,2-dimethyl-propionamide (23). Yield 66%, white solid. mp. 52 °C. ^{1}H-NMR $\delta(CDCl_3)$: 8.63 (s, 1H, pyrimidinyl-*H*), 8.58-8.51 (m, 2H, phenyl-*H*), 8.30-8.27 (m, 2H, phenyl-*H*), 8.21 (s, 1H, N-*H*), 7.54-7.51 (m, 6H, phenyl-*H*), 1.40 (s, 9H, C*H*$_3$)ppm. ^{13}C-NMR $\delta(CDCl_3)$: 178.0, 165.8, 163.8, 158.4, 137.3, 137.1, 130.7, 130.6, 128.6, 128.3, 128.1, 127.4, 103.2, 40.0, 27.2 ppm. MS (ES^+): 331.92 Da. Anal. ($C_{21}H_{21}N_3O$).

N-(2,6-Diphenyl-pyrimidin-4-yl)-3,3-dimethyl-butyramide (24). Yield 62%, white solid. mp.: 134 °C. ^{1}H-NMR $\delta(CDCl_3)$: 8.73 (br s, 1H, N-*H*), 8.64 (s, 1H, pyrimidyl-*H*), 8.55-8.50 (m, 2H, aromatic-*H*), 8.32-8.27 (m, 2H, aromatic-*H*), 7.54-7.49 (m, 11H,

aromatic-*H*), 2.20 (s, 2H, CH_2), 1.08 (s, 9H, 3*CH_3) ppm. ^{13}C-NMR $\delta(CDCl_3)$: 171.7, 165.9, 163.9, 158.4, 137.4, 137.1, 130.8, 130.7, 128.7, 128.4, 128.2, 127.4, 103.2, 51.0. 31.2, 30.0 ppm. MS (ES^+): 367.6 (MNa^+), 345.9 (MH^+) Da. Anal. ($C_{22}H_{23}N_3O$).

Cyclobutanecarboxylic acid (2,6-diphenyl-pyrimidin-4-yl)-amide (25). Yield 90%, white solid. mp.: 121-122 °C. ^{1}H-NMR $\delta(CDCl_3)$: 8.62 (s, 1H, pyrimidinyl-*H*), 8.56-8.51 (m, 2H, phenyl-*H*), 8.32-8.27 (m, 3H, phenyl-*H* + N-*H*), 7.54-7.48 (m, 6H, phenyl-*H*), 3.13 (pentet, 1H, -C*H*$CH_2CH_2CH_2$-), 2.45-1.90 (m, 6H, -CHC*H*$_2$C*H*$_2$C*H*$_2$-)ppm. ^{13}C-NMR $\delta(CDCl_3)$: 174.6, 165.8, 163.9, 158.4, 137.1, 130.7, 128.7, 128.4, 128.0, 127.4, 103.2, 86.9, 40.7, 24.9, 17.9ppm. MS (ES^+): 329.7 Da. Anal. ($C_{21}H_{19}N_3O$. 0.01H_2O).

Cyclopentanecarboxylic acid (2,6-diphenyl-pyrimidin-4-yl)-amide (26). Yield 69%, white solid. mp.: 126.5-127 °C. ^{1}H-NMR $\delta(CDCl_3)$: 8.60 (s, 1H, pyrimidinyl-*H*), 8.56-8.51 (m, 2H, phenyl-*H*), 8.32-8.26 (m, 3H, phenyl-*H* + N*H*), 7.53-7.50 (m, 6H, phenyl-*H*), 2.77-2.65 (m, 1H, -C*H*$CH_2CH_2CH_2CH_2$-), 1.98-1.60 (m, 8H, -CHC*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$-)ppm. ^{13}C-NMR $\delta(CDCl_3)$: 175.9, 165.8, 158.4, 137.4, 137.1, 130.7, 130.6, 128.7, 128.4, 128.0, 127.4, 103.2, 46.8, 30.2, 25.9ppm. MS (ES^+): 343.7 Da. Anal. ($C_{22}H_{21}N_3O$. 0.04H_20).

Cyclohexanecarboxylic acid (2,6-diphenyl-pyrimidin-4-yl)-amide (27). Yield 87%, white solid. mp.: 142-143 °C. ^{1}H-NMR $\delta(CDCl_3)$: 8.60 (s, 1H, pyrimidinyl-*H*), 8.57-8.52 (m, 2H, phenyl-*H*), 8.34 (bs, 1H, N*H*), 8.30-8.25 (m, 2H, phenyl-*H*), 7.53-7.49 (m, 6H, phenyl-*H*), 2.31-2.18 (m, 1H, -C*H*$CH_2CH_2CH_2CH_2CH_2$-), 1.97-1.30 (m, 10H, -CHC*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$-)ppm. ^{13}C-NMR $\delta(CDCl_3)$: 175.7, 165.8, 163.8, 158.4, 137.1, 130.7, 130.6, 128.6, 128.3, 127.3, 113.6, 103.2, 46.4, 29.2, 25.3ppm. MS (ES^+): 357.7, 358.7 Da. Anal. ($C_{23}H_{23}N_3O$. 0.15H_20).

Table 1 – Elemental Analysis

Compound No.	Molecular formula	Elemental Analysis		
		C%	H%	N%
15	$C_{23}H_{17}N_3O.0.25H_2O$ Calc.	77.61	4.81	11.80
	Found	77.61	5.07	11.88
16	$C_{18}H_{15}N_3O.0.5EtOH$	74.13	5.18	14.41
		74.06	5.57	14.40
17	$C_{19}H_{17}N_3O$	75.23	5.65	13.85
		75.32	6.23	14.04
18	$C_{20}H_{19}N_3O.\ 0.14H_20$	75.10	6.07	13.14
		75.09	6.29	13.28
19	$C_{20}H_{19}N_3O.\ 0.1H_2O$	75.26	6.00	13.16
		75.24	6.20	13.47
20	$C_{21}H_{21}N_3O$	76.13	6.34	12.69
		76.34	6.71	12.88
21	$C_{22}H_{23}N_3O.0.1H_2O$	76.10	6.68	12.10
		76.02	6.87	12.35
22	$C_{21}H_{21}N_3O$	76.13	6.34	12.69
		76.25	6.72	12.92
23	$C_{21}H_{21}N_3O$	76.11	6.39	12.68
		75.79	6.62	12.79
24	$C_{22}H_{23}N_3O$	76.49	6.71	12.16
		76.77	6.81	12.56
25	$C_{21}H_{19}N_3O.0.01H_2O$	76.53	5.81	12.75
		76.16	6.21	12.94
26	$C_{22}H_{21}N_3O.0.04H_2O$	76.78	6.15	12.21
		76.40	6.56	12.31
27	$C_{23}H_{23}N_3O.0.15H_2O$	76.70	6.44	11.67
		76.47	6.84	11.85

BIOLOGY

A primary function of certain cell surface receptors is to recognise appropriate ligands. Accordingly, we performed radioligand binding studies to establish the degree to which the compound binds to the receptor.

Radioligand Binding Studies [^{3}H]DPCPX was purchased from Amersham. All compounds made were tested in radioligand binding assays to determine their affinities at the human adenosine A_1 receptor. The affinities at the A_1 receptors were determined on CHO cells expressing the human receptors, using [^{3}H]DPCPX as the radioligand according to a previously described method.[11]

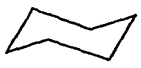
Data Analysis Competition binding data were fit to a single-site binding model and plotted using the software package Prism (Graph Pad, San Diego, CA, USA). The Cheng-Prusoff equation $K_i = IC_{50}/(1+[I]/K_d)$ was used to calculate K_i values, where K_i is the affinity constant for the competing ligand, [I] is the concentration of the free radioligand, and K_d is the affinity constant for the radioligand.

Structure Activity Relationships

In Table 2 results of the radioligand binding assays at the A_1 receptor are displayed, the substituents are defined hereinabove and below with reference to the compound of general formula (II). The reported literature focuses generally on bi-, and tri-cyclic heterocycles as the core structure about which substituents are varied. This monocyclic core with the 2,4,6-trisubstitution pattern has surprising efficacy at the adenosine A_1 receptor, as can be seen in Table 2. The compounds shown in Table 2 were also tested at

the adenosine A_{2A} and A_3 receptors and were shown to be generally selective for the adenosine A_1 receptor.

Table 2 – Radioligand Binding Assay

Comp	R	A_1[a]
15	Ph	671±113
16	CH_3	37.5±8.1
17	CH_2CH_3	9.50±4.6
18	$(CH_2)_2CH_3$	17.6±5.3
19	$CH(CH_3)_2$	11.1±6.2
20	$CH_2CH(CH_3)_2$	14.8±2.7
21	$CH(CH_2CH_3)_2$	6.35±0.4
22	$CH(CH_3)CH_2CH_3$	2.22±1.1
23	$C(CH_3)_3$	27.7±6.2
24	$CH_2C(CH_3)_3$	8.75±4.1
25		6.49±2.2
26		2.14±0.07
27		15.5±8.4

[a]Displacement of specific [^{3}H]DPCPX binding in CHO cells expressing human adenosine A_1 receptors. K_i (nM) ± SEM (n = 3).

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Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/NL04/000682

International filing date: 01 October 2004 (01.10.2004)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0323137.0
Filing date: 03 October 2003 (03.10.2003)

Date of receipt at the International Bureau: 22 March 2005 (22.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse